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Effectiveness of β-blocker therapy in daily practice patients with advanced chronic heart failure; is there an effect-modification by age?

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Aims
The effects of β-blockers in daily practice patients with advanced chronic heart failure (CHF) and a broad range of ejection fraction (EF) are not well established. We aimed to assess, first, the association between β-blocker prescription at discharge and mortality in a cohort of patients with advanced CHF, and second, whether this association is modified by the age of the patient.

Methods
Patients diagnosed with advanced CHF (n = 625) were prospectively followed after discharge from the Cardiology Department. The mean age was 76 years, 53% male, mean EF 42 ± 16%. Overall, 308 (49%) patients had a β-blocker prescribed at discharge, 140 (22%) low-dose and 168 (27%) high-dose therapy. We used multivariate Cox analysis to assess the association between β-blocker use at discharge and mortality.

Results
After a mean follow-up of 22 months, 117 (27%) patients died. Prescription of a β-blocker was associated with a 45% relative risk reduction (hazard ratio 0.55, 95% confidence interval 0.39, 0.78). The relative risk reduction was similar with low and high doses of β-blockers (42% and 49%). However, the relative risk reduction was higher in younger than in older patients (P = 0.006). In patients ≤75 years old prescription of a β-blocker was associated with 71% risk reduction, whereas in patients >75 years old it was associated with 21% risk reduction.

Conclusions
In this daily practice cohort of patients with advanced CHF, prescription of a β-blocker was associated with significant mortality reduction. However, the beneficial effects of β-blockers appear to be greater in younger patients.

Introduction

Several randomized trials have shown that β-blockers reduce mortality in patients with advanced chronic heart failure (CHF) and depressed ejection fraction (EF) [1–3]. However, compared with participants in clinical trials, patients in clinical practice are generally older, more often female, and are more likely to have comorbid conditions [4, 5]. Furthermore, approximately 30–50%

of patients have a normal or nearly normal EF [6]. In addition, treatment with β-blockers is frequently prescribed at doses lower than those investigated in clinical trials, probably attributable to concern about its tolerability in the elderly [7, 8]. Thus, the effectiveness of β-blocker medication in real-world practice of advanced CHF remains uncertain.

Findings in patients with moderate to advanced CHF and a broad range of EF are inconclusive. The SENIORS trial showed that the β-blocker nebivolol reduces the risk of death in patients older than 70 years, regardless of EF. However, the risk reduction is lower compared with younger patients with depressed EF [9]. One observational study has shown that prescription of a β-blocker is not a significant predictor of mortality in patients older than 75 years, irrespective of EF [10]. In contrast, two other cohort studies that assessed the effect of β-blockers in elderly patients (age >65 years) with a broad range of EF have reported a benefit on mortality similar to that obtained in clinical trials (~30% risk reduction) [7, 11]. This leaves the question to what extent the effectiveness of β-blockers is modified by the age of the patient.

In this study, we aimed to assess, first, the association between β-blocker prescription at discharge and mortality in a daily practice cohort of patients with advanced CHF, and second, whether this association is modified by the age of the patient.

Methods

Patients

Patients were selected at the Cardiology Department of Rijnland General hospital, Leiderdorp, the Netherlands, between January 2000 and July 2004. Patients admitted to hospital with CHF New York Heart Association (NYHA) class III and IV, age ≥45 years, were included in the study. Referral of patients for admission was made by general practitioners, other units of the hospital or the outpatient clinic. HF with reduced systolic function was diagnosed on the basis of clinical presentation (signs and symptoms of HF) and presence of systolic functional impairment by echocardiography (EF ≤40%). HF with preserved systolic function was defined based on clinical symptoms, radiographic evidence of HF, and EF >40% [12]. EF was assessed by 'eyeball' estimate. All patients gave informed consent for the study, which was approved by the local medical ethics committee.

Medication and clinical variables

Demographic characteristics, clinical data and medication prescribed at discharge were collected prospectively from the patients' files. As β-blockers are usually prescribed in multiple drug combinations, the following classes of medication were considered for adjustment: angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), aldosterone antagonists, loop diuretics, digitalis, calcium-channel blockers, antiarrhythmics, nitrates and coumarins. Moreover, to distinguish between the effect of low- and high-dose therapy, β-blockers, ACEI, spironolactone and loop diuretics were classified into one of the three mutually exclusive groups: not dispensed, low or high dose. A low dose of β-blockers and ACEI was defined as <50% of the target dose achieved in randomized controlled trials (RCTs); a higher dose was defined as ≥50% of the dose used in RCTs (Table 1) [7]. After discharge, we considered medication constant during follow-up.

Table 1
Classification of low and high doses of β-blocker, angiotensin-converting enzyme inhibitors (ACEI), spironolactone and loop diuretics

	Dose range (mg day^{-1})	
Drug (Reference)	Low dose	High dose
β-Blockers		
Carvedilol	<25	≥25
Metroprolol	<100	≥100
Bisoprolol	<5	≥5
Nebivolol	<5	≥5
Labetalol	<1200	≥1200
Propranolol	<80	≥80
Atenolol	<50	≥50
ACEIs		
Enalapril	<10	≥10
Captopril	<75	≥75
Lisinopril	<10	≥10
Fosinopril	<10	≥10
Quinapril	<20	≥20
Perindopril	<4	≥4
Ramipril	<5	≥5
Loop diuretics		
Furosemide	≤80	>80
Bumetanide	≤2	>2
Spironolactone	≤25	>25

A low dose ofβ-blocker and ACEI is defined as <50% of the target dose attained in randomized clinical trials. A low dose of spironolactone is defined as ≤50% of the target dose attained in randomized clinical trials. A low dose of loop diuretics is defined as furosemide ≤80 mg, bumetanide ≤2 mg.

Clinical characteristics considered as candidate variables for adjustment included: age, gender, history of hypertension or myocardial infarction (MI), severity of CHF assessed by NYHA class and EF, heart rate, mean arterial pressure, renal function assessed by glomerular filtration rate (GFR), haemoglobin levels and comorbidities such as diabetes, chronic obstructive pulmonary disease (COPD), stroke or atrial fibrillation (AF). GFR was calculated using the Cockroft–Gault equation: [(140 − age in years) × (body weight in kg)]/serum creatinine in μmol l^{-1}. In men, the value is multiplied by 1.25 [13]. Mean arterial pressure was calculated as the sum of 2/3 diastolic blood pressure and 1/3 systolic blood pressure. Anaemia was defined as haemoglobin <8.5 mmol l^{-1} for men and <7.5 mmol l^{-1} for women.

Haemoglobin levels were missing in 41 patients (6%) and the values were obtained by mean imputation. Forty-nine patients (7%) who missed EF at discharge and 17 patients (3%) transferred to other departments were excluded from the analysis.

Outcomes

Clinical outcome included all-cause mortality. Follow-up was calculated from the date of discharge until September 2004. Deaths during follow-up were obtained from hospital records, next-of-kin review or by telephone.

Statistical analysis

Differences among patient subgroups were evaluated by using ANOVA or χ^2 test, as appropriate.

To assess the association between β-blocker prescription and mortality during follow-up multivariate Cox proportional hazard models was used. We controlled for baseline characteristics that had an independent association with mortality ($P < 0.3$) and for important risk variables identified in previous studies (EF and NYHA class). To minimize selection bias, we also adjusted for propensity score of β-blocker use [14]. For each patient, a propensity score indicating the likelihood of having prescribed a β-blocker was calculated by forward logistic regression. Baseline characteristics that had an independent association with prescription of a β-blocker ($P < 0.3$) were included in the multivariate logistic model. Goodness-of-fit of the propensity score was evaluated by the Hosmer–Lemeshow test and discrimination by the c statistic. Linearity of continuous variables was checked, resulting in only mean arterial pressure being included as a continuous variable in the model.

To assess whether there is effect modification by age, a secondary analysis including interaction terms was performed. The risk of death was presented by hazard ratios (HR) with 95% confidence intervals (95% CI). All reported probabilities were two-tailed, and a *P*-value <0.05 was considered statistically significant. Data were analysed with SPSS version 12.0 software (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

The total cohort at discharge included 625 patients; approximately half were female (Table 2). Patients were elderly, with a mean age of 76 years (median 78 years, 90% reference range 56–90). Nearly 64% were in NYHA III and 36% in NYHA IV. The mean EF was 42 ± 16% (45% having EF >40%). Approximately 44% had a history of MI and 45% had a history of hypertension. The prevalence of diabetes, AF and COPD was 30%, 40% and 30%, respectively. About half of the patients had severe renal dysfunction (GFR <40 ml min^{-1}).

Medication at discharge

Overall, 308 (49%) patients had a β-blocker prescribed at discharge, with 140 (46%) receiving low-dose therapy and 168 (54%) high-dose therapy (Table 2). Patients receiving high doses of β-blockers were more often younger, female, had a higher mean arterial pressure and a higher prevalence of preserved EF. Conversely, they had a lower prevalence of COPD, low sodium serum levels and renal dysfunction. Patients on high-dose β-blockers received less often high doses of loop diuretics and spironolactone. Users of β-blockers received more nitrates and aspirin, and less antiarrhythmics, digoxin and coumarins than non-users.

Mortality outcome

The mean duration of follow-up was 22 (±15) months. Death (all causes) occurred in 54 (17.5%) patients on a β-blocker and 117 (37%) patients without a β-blocker. Overall, 171 (27%) patients died during a median follow-up of 8 months.

In univariate analysis, the following variables were associated with a higher risk of death: older age, male gender, lower mean arterial pressure, COPD, lower sodium serum, lower GFR, nonprescription of a β-blocker (either low or high dose) or aspirin, and prescription of loop diuretics (high dose), spironolactone (high dose), antiarrhythmics and digoxin (Table 3).

Propensity score analysis

Patients were more likely to be prescribed β-blockers if they were younger, had higher systolic blood pressure, or had a nitrate or aspirin prescribed. In contrast, β-

Table 2
Baseline characteristics of the study population

Variables	Total cohort (n = 625)	No β-blockers (n = 317)	β-blockers low dose (n = 158)	β-blockers high dose (n = 150)	P-value for trend
Age, years, mean (SD)	76 (10)	77 (9)	77 (11)	75 (10)	0.03
>75 years (%)	59	64	55	54	0.03
Gender (% female)	47	43	48	53	0.05
History of myocardial infarction (%)	44	43	44	45	0.7
History of hypertension (%)	45	38	49	57	<0.001
NYHA (% IV)	36	38	36	32	0.2
LVEF, mean (SD)	42 (16)	42 (16)	38 (15)	47 (15)	<0.001
>40% (%)	45	45	37	56	0.08
Heart rate >100 beats min^{-1} (%)	45.4	45.0	48.6	42.9	0.8
Mean arterial pressure, mmHg (SD)	102 (22)	97 (20)	104 (22)	108 (25)	<0.001
Diabetes (%)	29	27	31	30	0.5
Atrial fibrillation (%)	39	42	36	36	0.1
COPD (%)	29	36	24	19	<0.001
Sodium serum <137 mmol l^{-1} (%)	19	22	19	14	0.06
Haemoglobin <8.5/7.5 mmol l^{-1} (%)	44	46	43	42	0.3
GFR <40 ml min^{-1} (%)	48	49	51	43	0.2
Medication at discharge (%)					
ACE inhibitors					0.8
Low dose	37	39	40	26.7	
High dose	33	29	36	35	
ARB	11	11	8	16	0.2
Loop diuretic					0.05
Low dose	61	57	68	61	
High dose	27	30	25	22	
Spironolactone					0.03
Low dose	28	27	31	27	
High dose	10	13	9	6	
Digoxin	23	29	16	17	<0.001
Antiarrhythmic	24	34	13	16	<0.001
Nitrates	50	42	55	61	<0.001
Calcium-channel blockers	14	14	8	20	0.2
Coumarin	56	62	54	47	0.001
Aspirin	29	22	32	42	<0.001

NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary diseasse; GFR, glomerular filtration rate; ARB, angiotensin receptor blocker. A low dose of angiotensin-converting enzyme inhibitor andβ-blocker is defined as <50% of the target dose attained in randomized clinical trials. A low dose of loop diuretics is defined as furosemide ≤80 mg, bumetanide ≤2 mg. A low dose of spironolactone is defined as ≤25 mg.

blockers were less likely to be prescribed if patients had COPD or had an antiarrhythmic or digoxin prescribed. The model had a good discriminatory power and good fit (c-statistics, 0.75; overall goodness-of-fit Hosmer–Lemeshow test; $\chi^2 = 7.1$, $P = 0.5$).

Multivariate analysis

After adjustment for clinical variables and propensity scores, β-blocker use remained associated with a 45% relative reduction in the risk of death (HR 0.55, 95% CI 0.39, 0.78) (Table 4). The relative risk reduction was similar with the prescription of low or high doses of β-blockers, 42% and 49%, respectively (HR 0.58, 95% CI 0.38, 0.88, $P = 0.01$; HR 0.51, 95% CI 0.31, 0.82, $P = 0.006$) (results not shown). The absolute risk reduction (ARR) (derived from Cox survival curves) was as follows: 5% at 6 months, 8% at 1 year and 10% at 2 years. The number needed to treat (NNT = 1/ARR) to

Table 3
Univariate Cox relation between clinical characteristics and all-cause mortality

Variables	Alive (n = 454)	Dead (n = 171)	Hazard ratio (95% CI)	P-value
Age, years, mean (SD)	77 (10)	78 (9)	1.02 (1.01, 1.04)	0.02
>75 years (%)	60	65	1.3 (0.9, 1.9)	0.1
Gender (% female)	50	40	0.7 (0.5, 0.9)	0.02
History of hypertension (%)	46	40	0.8 (0.6, 1.2)	0.2
NYHA (% IV)	35	42	1.1 (0.8, 1.6))	0.5
LVEF, mean (SD)	43 (16)	41 (18)	0.9 (0.98, 1.01)	0.4
>40% (%)	46	42	0.9 (0.6, 1.2)	0.4
Mean arterial pressure, mmHg (SD)	103 (22)	96 (21)	0.9 (0.97, 0.99)	<0.001
Atrial fibrillation (%)	40	36	0.9 (0.6, 1.3)	0.5
COPD (%)	27	33	1.3 (0.9, 1.8)	0.2
Sodium serum <137 mmol l^{-1} (%)	17	28	1.7 (1.2, 2.5)	0.005
GFR <40 ml min^{-1} (%)	46	62	1.9 (1.4, 2.7)	<0.001
Medication at discharge (%)				
ARB	11	13	1.1 (0.7, 1.9)	0.6
β-Blocker				
Low dose	28	17	0.5 (0.3, 0.7)	0.001*
High dose	27	14	0.4 (0.3, 0.7)	0.001
Loop diuretic				
Low dose	66	46	1.1 (0.6, 1.9)	0.8
High dose	21	44	2.8 (1.6, 5.1)	0.001
Spironolactone				
Low dose	28	29	1.2 (0.8, 1.8)	0.3
High dose	10	14	1.4 (0.8, 2.3)	0.2
Digoxin	22	28	1.3 (0.9, 1.9)	0.2
Antiarrhythmic	22	30	1.4 (0.9, 1.9)	0.09
Nitrates	49	51	1.1 (0.8, 1.5)	0.6
Calcium-channel blockers	13	15	1.1 (0.6, 1.7)	0.8
Coumarinic	55	60	1.2 (0.9, 1.6)	0.3
Aspirin	32	23	0.7 (0.5, 0.9)	0.04

**The reference value for all classes of medication with doses was medication not dispensed. NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; ARB, angiotensin receptor blocker. A low dose of β-blocker is defined as <50% of the target dose attained in randomized clinical trials. A low dose of loop diuretics is defined as furosemide ≤80 mg, bumetanide ≤2 mg. A low dose of spironolactone is defined as ≤25 mg.*

avoid one death was as follows: 20 patients for 6 months, 12 patients for 1 year and 10 patients for 2 years.

However, in the secondary analysis for interaction effects, we found a different effect of β-blocker medication in patients younger and older than 75 years (P = 0.006). No other interaction remained significant in the final model. In patients aged ≤75 years prescription of a β-blocker was associated with a 71% relative risk reduction, while in patients >75 years it was associated with 21% relative risk reduction (Table 4). For both age groups, a similar effect was observed with prescription of low- or high-dose β-blocker. Loop diuretics in high dose were significantly associated with a twofold increase in the risk of death. Prescription of spironolactone (high dose) was associated with about 30% reduction in the risk of death (nonsignificant). Clinical variables significantly associated with an increased risk of death were male gender, lower GFR and lower mean arterial pressure (Table 4).

In our study population, patients >75 years old comprised more women, had significantly higher EF, more AF, less MI, lower GFR and lower haemoglobin concentrations, compared with patients <75 years old

Table 4
Multivariate relationship between clinical variables, medication use and all-cause mortality*

Variable	*N* (%)	Adjusted HR	95% CI	*P*-value
β-Blockers†	308 (49)	0.55	0.39, 0.78	0.001
β-Blockers				
Age ≤75 years	140 (46)	0.29	0.16, 0.53	<0.001
Age >75 years	168 (54)	0.79	0.52, 1.20	0.3
Loop diuretics				
Not prescribed	75 (12)	1.00	–	–
Low dose	382 (61)	1.14	0.64, 2.04	0.6
High dose	168 (27)	1.95	1.05, 3.61	0.03
Gender (female)	292 (47)	0.67	0.47, 0.95	0.02
GFR < 40 ml min^{-1}	300 (48)	2.08	1.47, 2.94	<0.001
Mean arterial pressure	625 (100)	0.99	0.98, 0.99	0.007

**Adjusted for age, gender, New York Heart Association class, ejection fraction, chronic obstructive pulmonary disease, hypertension, sodium serum, concomitant medication, and propensity scores for β-blocker use. †β-Blocker effect in the whole population; prescription coded as yes/no, as prescription of high or low doses of β-blocker was associated with a similar reduction in the risk of death. GFR, Glomerular filtration rate.*

(results not shown). The majority of patients were treated with a β-blocker tested in clinical trials (carvedilol, metoprolol or bisoprolol). No significant differences in the type of β-blocker prescribed in patients older and younger than 75 years were seen, although older patients were prescribed less carvedilol (Table 5).

Table 6 shows the relative risk reduction associated with prescription of a β-blocker, at different ages. The data show a linear trend within the range of 65–85 years, which includes most of our patients. While in a patient of 65 years the risk reduction is about 70%, in a patient of 75 years it is 50% and in a patient of 80 years about 40%.

Table 5
Type of β-blocker prescribed per age category

β-Blocker type	All population* (*N* = 308)	Age ≤ 75 (*N* = 140)	Age > 75 (*N* = 168)
Carvedilol	129 (41.9)	64 (45.7)	65 (38.7)
Metoprolol succinate	84 (27.3)	39 (27.9)	45 (26.8)
Metoprolol tartrat	52 (16.9)	21 (15.0)	31 (18.5)
Bisoprolol	33 (10.7)	11 (7.9)	22 (13.1)
Atenolol	7 (2.3)	3 (2.1)	4 (2.4)
Labetalol	1 (0.3)	1 (0.7)	–
Nebivolol	1 (0.3)	–	1 (0.6)
Propranolol	1 (0.3)	1 (0.7)	–

Data are presented as n *(%). *All the population of patients who received a β-blocker.* P-*value age ≤75* vs. *age >75 years nonsignificant for all types of β-blocker.*

Discussion

In this daily practice cohort of advanced CHF patients, prescription of a β-blocker was associated with a 45% relative mortality risk reduction. The risk reduction decreased with age from 71% in patients ≤75 years to 21% in the older ones.

Our findings in advanced CHF patients are consistent with those of the SENIORS trial, which documented the benefit of β-blocker nebivolol in elderly patients (age >70 years) with moderate to advanced CHF [9]. The study showed that addition of nebivolol to conventional treatment was associated with a 12% relative risk reduction, a lesser degree of benefit, compared with that reported in younger patients with CHF and depressed EF (30% risk reduction). The risk reduction with β-blockers in our cohort was slightly higher than that reported in SENIORS, probably as a result of the higher mortality in our study, which enrolled unselected patients with advanced CHF.

Our results are also similar to those of a previous

Table 6
Relative reduction of mortality associated with prescription of a β-blocker, per age*

Variable	Adjusted HR	95% CI
Age (years)		
65	0.31	0.15, 0.64
70	0.38	0.20, 0.71
75	0.47	0.26, 0.83
80	0.57	0.32, 1.02
85	0.70	0.37, 1.34

**Adjusted for gender, New York Heart Association class, ejection fraction, mean arterial pressure, chronic obstructive pulmonary disease, sodium serum, glomerular filtration rate, concomitant medication and propensity scores for β-blocker use.*

population-based cohort study in patients with moderate to advanced CHF; patients who received low-dose β-blocker therapy (<50% of trial dose) had a similar survival to those receiving higher doses [7]. A similar benefit on survival with dispensing of low- or high-dose β-blocker therapy has been also reported in the MERIT-HF trial [15].

Although the overall effect on mortality observed with β-blockers in our population was similar to that observed in previous cohort studies [7, 11], the effect modification by age has not been reported before. Inclusion of patients with advanced CHF, as well as adjustment for doses of a broad range of CHF medication, may explain the different age-related effect observed in our population.

The reduced benefit of β-blocker therapy in the elderly may have several explanations. First, this group had a significantly higher prevalence of preserved EF. In patients with CHF and preserved EF, autonomic function and neurohormonal activation are less severely affected [16–18]. A previous study in the SOLVD registry has shown that patients with EF <45% have higher levels of plasma norepinephrine and atrial natriuretic peptides compared with those with EF >45% [19]. Conversely, another study reported similar concentrations of plasma norepinephrine, but also higher concentrations of brain and atrial natriuretic peptides in patients with systolic HF compared with those with diastolic dysfunction [16]. Sympathetic nervous system activation in CHF is a major contributor to the disease, and β-blockers benefit primarily via antagonism of its effects [20, 21]. β-blockers may also benefit via reduction in heart rate and blood pressure, as well as reduction of arrhythmias [22]. It is possible that a lower sympathetic activation in the CHF with preserved EF may partly explain a lesser degree of benefit from β-blocker therapy.

Second, a decreased response to β-blocker therapy may occur in the elderly [23–25]. Altered drug actions in older people are mainly attributed to age-related pharmacodynamic changes, such as alterations in receptor density and sensitivity, endocrine activation and changes in the autonomic nervous system. Such changes appear in particular after the age of 70. However, a previous meta-analysis in patients with systolic HF has shown that older patients (>60–70 years) derive as much benefit from β-blockers as those that are younger [26]. Nevertheless, exclusion of patients >75–80 years old from the clinical trials may account for the nonsignificant difference, as a 10% lower relative risk reduction in older patients compared with the younger ones was reported.

Third, older patients had a higher prevalence of AF and associated comorbidities. Retrospective analysis in the CIBIS II study showed no survival benefit of bisoprolol in CHF patients with poor systolic function and AF, unlike those in sinus rhythm [27]. Some other studies have debated that β-blockers may have less effect on symptoms and exercise capacity in patients with CHF and AF when compared with those in sinus rhythm [28].

Finally, it may be that the increased risk of dying from multiple causes (including biological age) in the elderly compete with a potential benefit of β-blocker medication. That is, a patient of 80 years may have a life expectancy of 5 years, so that the medication cannot achieve the same benefit as in a 10 years younger patient. Age itself may therefore be considered a confounder, although in our population age was not an independent predictor of mortality.

After adjustment, prescription of loop diuretics in high dose remained independently associated with an increased risk of death. The deleterious effects of loop diuretics are mainly explained through K+ excretion-related complications and activation of the renin–angiotensin–aldosterone system, as a result of volume depletion [29, 30].

Our study examined clinical issues for which existing clinical trials do not provide guidance. First, the results indicate a beneficial effect of β-blockers on mortality in patients with advanced CHF. The NNT shows the high effectiveness of the treatment, with only 20 patients necessary to treat for 6 months to avoid one event. The beneficial effects of β-blockers appear to be higher in patients <80 years old. Interventions must be therefore

conducted to improve prescription of β-blockers in this age group, as the actual prescription rate (about 50%) is much less than optimal. In older patients, prescription of β-blockers may also deserve consideration. Although on average an effect on mortality in these patients is not clear, a benefit on the composite measure of mortality and readmission may be achieved (as shown in the SENIORS trial). Nevertheless, more clinical trials and observational studies are warranted to provide a clear answer on the benefit of β-blockers on mortality in elderly patients with advanced CHF. Second, our study provides information on the benefit of low-dose β-blocker therapy. This may encourage clinicians to prescribe low doses of β-blockers when high doses cannot be achieved.

Our study has a number of limitations. First, because β-blocker treatment was not randomized, other risk factors may have played a role. To address this issue, we adjusted for many variables and used statistical techniques to minimize selection bias. Second, cardiovascular and not overall mortality may be a more relevant end-point in the elderly, who are at high risk of death from multiple causes. Nevertheless, a distinction between cardiovascular and noncardiovascular causes of death in elderly patients with CHF is in many instances difficult. Third, we assumed that medication prescribed at discharge was constant during follow-up. Prior studies have shown that patients discharged without a prescription of a β-blocker or ACEI are unlikely to be started on these therapies as outpatients [31, 32]. However, in patients who are discharged on these therapies, there is a decline in use after discharge. If this is the case, the effect of β-blockers in our study might be overestimated, although we think not to a great extent. To account for a potential change in medication during follow-up readmissions, we performed the analysis without readmitted patients (17% of the total population) and the results were similar.

In conclusion, in this cohort of patients with advanced CHF in daily practice, prescription of a β-blocker was associated with a significant reduction in mortality. However, the beneficial effects of β-blockers appear to be greater in younger patients.

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